IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

101195-64

SERIAL NO.	:	09/980,645
APPLICANT	:	Stefan Anker et al
FILED	:	March 20, 2002
EXAMINER	:	Phuong N. Huynh
ART UNIT	:	1644
FOR	:	THERAPY AND USE OF COMPOUNDS IN THERAPY

DECLARATION UNDER 37 C.F.R. § 1.132

Hon. Assistant Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, the undersigned declarant, hereby declare as follows:

I am a named inventor in the above-referenced application;

I am a German citizen and a reside in Berlin, Germany;

My *curriculum vitae* is attached

Based on the teachings of the specification, I and the co-inventors conducted the experiments attached as **Exhibit 3** set forth in detail in the attached description, and I submit this declaration in support of the above-referenced application.

All statements made herein on knowledge are true, and all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statement and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date:

Stefan Anker

CURRICULUM VITAE – 22. September 2005

Stefan D. Anker, MD PhD
Professor of Applied Cachexia Research

Personal Details

- born September 19th 1965 in Berlin
- married since July 31st 1987 (wife: design engineer), 1 son (born May 3rd 1989)
- Nationality: German; Citizenship: Germany
- address: prof./Berlin Division of Applied Cachexia Research, Dept of Cardiology,
Charité Campus Virchow-Klinikum, Augustenburger Platz 1, D-13353 Berlin, Germany.
Tel (+49) (30) 450 55 3463; Fax (49) (30) 450 55 3951
prof./London Clinical Cardiology, NHLI, Dovehouse Street, London SW3 6LY, UK.
Tel (+44) (20) 7351 8203; Fax (44) (20) 7351 8733
Private: Mahlerstraße 13, D-13088 Berlin, Germany.
Tel (+49) (30) 9606 5600; Fax (+49) (30) 9606 5603
E-mail s.anker@imperial.ac.uk

Education/Degrees

- 07.07.84: Gymnasium in Berlin, Abitur, *average grading: 1.55*
- 11/87-7/93: medical studies, Medical School (Charité) of Humboldt-University Berlin, Germany
- 30.07.93: final exams of medical studies
- 29.10.93: MD for the thesis "Epidemiology of cholelithiasis in the GDR - hospital morbidity and mortality 1969 to 1989", *cum laude*
- 1/95-12/97: registered PhD student, NHLI at Imperial College of Science, Technology and Medicine
- 01.06.95: "Approbation als Arzt" (i.e. full registration in Germany)
- 06.02.96: GMC full registration (No. 4267865)
- 28.2.98: PhD for the thesis "Studies of cachexia complicating chronic heart failure" (supervisor Prof. AJS Coats, sponsor Prof. PA Poole-Wilson)
- 09.07.04: Specialist Registration (Facharzt) "Cardiac Myology" (via accademic pathway) GMC reference: 4267865

Professional Experience

- "Arzt im Praktikum" phase (12/93 - 5/95) : Dept. of Cardiology, Charité Campus Mitte, Berlin, Germany
- 6-12/95: Assistant Doctor, Dept of Anaesthesiology, Charité Medical School, Berlin, Germany
- 8/94-2/95: Research Fellow, Dept of Cardiology, NHLI London
- 1/96-12/97: Research Registrar and PhD student at NHLI London and Royal Brompton Hospital, London
- since 1/98: Senior Research Fellow and Team Leader at the NHLI London / Imperial College (continuing)
- 7/98-6/02: Assistant Doctor, Dept of Cardiology, Franz-Volhard-Klinik (Charité Campus Berlin-Buch) at Max Delbrück Center for Molecular Biology (MDC Berlin-Buch), Berlin, Germany
- since 7/02: Professor for Applied Cachexia Research, Dept of Cardiology, Charité Campus Virchow-Klinikum, Berlin, Germany (continuing)
- since 11/03: Visiting Professor, University of Sydney School of Medicine (continuing)

Teaching Experience

- regularly medical student, and diploma and MSc student courses in London: since 1996
- registered teacher status at London of London and Imperial College (for independent PhD supervision), since 2003
- numerous invited lectures (see list of publications)
- supervision of MD students in Berlin: currently 8 Dr.med./Dr.vet.med/Dr.rer.nat. students in Berlin at various stages (1 MD thesis under review)
- co-supervision/supervision postgraduate students in London: 3 finished PhD's (M Rauchhaus, R Sharma, W Doehner), currently 3 PhD students and 1 MD student at various stages

Awards/Grants

- 05.10.90: "Gerhardt-Katsch-Stipendium", German Society of Gastroenterology
- 12/93+12/95: Research Grant of the Charité Medical School Berlin
- 7/94+8/95: Research Fellowship, "Ernst und Bertha Grimmke" Foundation, Germany (11 months)
- 10/96-3/97: Research Fellowship of the European Society of Cardiology (6 months)
- 4/97: Runner-up UK Junior Cardiac Club Competition, Clinical Cardiology
- 4/98: MDC Berlin Postgraduate Fellowship for 1999 and 2001 (24 months)
- 6/98: Research Grant, Garfield-Weston Trust Fund
- 22.10.98: "Ehrenmedalie der Charité Berlin" (honoary medal of the Charité medical school, Berlin)
- 11/98: Runner-up; Samual A Levine Young Investigators Award, AHA Conference 1998: *Niebauer J, Poole-Wilson PA, Coats AJS, Anker SD. Endotoxin and immune activation in chronic heart failure: proof of concept*
- 3/99: 2nd Prize; ACC Young Investigators Award Clinical Cardiology, ACC meeting 1999: *Ponikowski P, Anker SD, Coats AJS. Oscilatory breathing patterns during the wakefulness in patients with chronic heart failure: clinical and prognostic implications.*
- 8/00: 3rd Prize, Young Investigator Award Clinical Cardiology, European Society of Cardiology: *Anker SD, Negassa A, Coats AJS, Poole-Wilson PA, Yusuf S. Prognostic importance of weight loss in chronic heart failure and the impact of treatment with ACE inhibitors.*
- 11/00: Winner, Samual A Levine Young Investigators Award, AHA Conference 2000: *Sharma R, Coats AJS, Anker SD. Cellular endotoxin responsiveness in patients with chronic heart failure.*
- 02/01: GlaxoSmithKline Respiratory Clinical Research Award *"Cellular endotoxin responsiveness in patients with chronic obstructive pulmonary disease and its relationship to the development of cachexia."*
- 02/02: Vandervelle Foundation Fellowship Award
- 07/02: Juniorprofessorship Development Grant, Charité Berlin
- 09/02: Juniorprofessor Startup Grant, Ministery for Education and Science, Germany
- 08/03: Syner-Med Scholarship "Studies on anaemia in heart failure"
- 06/04: University of Sydney research grant "Cachexia research"
- 08/04: NIH research grant "WARCEF study – patients recruitment in Germany and Poland"
- 09/05: NIH research grant "WARCEF study – patients recruitment in Netherlands"

Publications

- >160 original papers, reviews and editorials (>2500 citations)
- >300 abstracts
- >250 invited lectures

Editorial Boards

- Journal of Cardiac Failure (since 2002)
- Italian Heart Journal (since 2003)
- International Journal of Cardiology (Associated Editor for Metabolic Cardiology, since 2004)
- Zeitschrift für Kardiologie (Germany, since 2004)

Professional Body Memberships

- German Society of Cardiology
- European Society of Cardiology,
- ESC Heart Failure Association
- American Heart Association, Council of Clinical Cardiology

Journal Reviewing

I have worked for 26 different scientific journals:

American Journal of Cardiology, American Journal of Cardiovascular Drugs, American Journal of Physiology, Basic Research in Cardiology, Blood Coagulation & Fibrinolysis, Chest, Circulation, Circulation Research, Clinical Science, Drugs, European Heart Journal, Europace, European Journal of Cardiovascular Rehabilitation, European Journal of Endocrinology, European Journal of Heart Failure, Heart, International Journal of Cardiology, JAMA, Journal of American College of Cardiology, Journal of Applied Physiology, Journal of Cardiac Failure, Journal of Gerontology, Journal of Hypertension, New England Journal of Medicine, Journal of the American Geriatrics Society, The Journals of Gerontology.

Grant Reviewing

North-Irish Chest, Heart & Stroke Association (2003), British Heart Foundation (2003), Italian Cancer Research Association (2003), Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung (2003/04), European Commission (for FP6-2004-LIFESCIHEALTH-5 call) (2004/05)

Thesis Reviewing

University of Melbourne, Faculty of Medicine (for PhD) (2004)
University of Perth, Faculty of Medicine (for PhD) (2005)
Charité Berlin (for Dr.med.)

Steering Committees

1. SENIORS trial (Nebivolol in CHF M+M trial, coordinator for Germany)
2. UNIVERSE trial (Rosuvastatin in CHF for cardiac function)
3. GISSI-HF international advisory board (Fish oil and rosuvastatin in CHF M+M trial, coordinator cardiac

cachexia substudy)
4. Amgen 126 (Darbepoietin alpha in CHF for exercise capacity, co-PI London)
5. ACCLAIM trial (Celecade immune modulation in CHF M+M trial, coodinator for Germany)
6. WARCEF trial (Warfarin vs Aspirin in CHF M+M trial, coordinator for Germany)

Effect of Ursodeoxycholic Acid (UDCA) on Peripheral Blood Flow, Immune Function and Markers of Neurohormonal Activation and Cardiac Function in Patients with Chronic Heart Failure: A Randomised, Placebo-Controlled, Double-Blind Cross-Over Study (UDCA-HF)

Stephan von Haehling [1,2], Ewa A. Jankowska [2,3], Wolfram Doehner [1,2], Wolfram Steinborn [2], Ali Vazir [2], Darlington O Okonko [2], Hans-Dieter Volk [4], Philip A Poole-Wilson [1], Stefan D Anker [1,2]

[1] Department of Cardiology, Charité Campus Virchow-Klinikum, Berlin, Germany.
[2] Clinical Cardiology, NHLI, Imperial College London, London, UK.
[3] Cardiac Department, Military Hospital, Wroclaw, Poland
[4] Department of Immunology, Charité Campus Mitte, Berlin, Germany.

Background: Inflammation contributes to the development of endothelial dysfunction and is related to increased mortality in patients with chronic heart failure (CHF). Endotoxin, a bacterial cell wall component, may enter the circulation through the oedematous gut wall, and could be the causal trigger for inflammatory cytokine production in CHF patients. Bile acids, like ursodeoxycholic acid (UDCA) can bind to endotoxin in micells and thereby inhibit endotoxin absorption through the gut wall and block the interaction of endotoxin with immune-competent cells. UDCA could also improve liver function. We tested the hypothesis that treatment with ursodeoxycholic acid (UDCA) would improve endothelial and immune function in CHF patients.

Methods: In a placebo-controlled, double-blind, cross-over study, 16 male CHF patients (age 66±3y, 75% ischemic etiology, all NYHA class II-III, LVEF 31±2% [all <45%], creatinine 131±13 µmol/L, white blood cell count [WBC] 6.9±0.5 x10^9/L) were treated with UDCA 500 mg twice daily for 4 weeks and with placebo for 4 weeks. Treatments were provided in random order with a 4-week wash out period in-between. All patients received optimal drug treatment with ACE inhibitors and/or angiotensin receptor blockers (94%), beta-blockers (69%) and spironolactone (75%). As a measure of endothelial function, arm (primary endpoint) and leg blood flow was assessed using venous occlusion strain gauge plethysmography at rest and after 3 min ischemia (peak flow).

Results: Treatment with UDCA improved arm peak flow compared to placebo by 18% (26.4±2.0 vs 22.3±1.6 mL/100 mL/min, p=0.038) and leg peak flow by 17% (16.5±2.3 vs 14.1±1.4, p=0.079). Blood flow at rest remained unchanged (p>0.7). UDCA decreased WBC (6.9±0.4 vs 7.6±0.4, p=0.0075), absolute neutrophil (4.6±0.4 vs 5.1±0.4, p=0.025), and lymphocyte count (1.5±0.1 vs 1.7±0.1, p=0.013) compared to placebo. UDCA decreased plasma values of gamma-glutamyl transpeptidase (GGT, 29±3 vs 37±6, p=0.0094) compared to placebo. No serious adverse events were observed.

Conclusions: UDCA safely improves endothelial function, improves aspects of liver function and has anti-inflammatory effects as evidenced by reduced

levels the number of circulating neutrophils and lymphocytes in patients with chronic heart failure.

Endothelial dysfunction is a marker of poor prognosis in CHF, and drugs that improve endothelial function are very likely to have general benefits on morbidity and mortality.